Remarks

Claims 1-22 are pending. Claims 15-22 have been withdrawn from consideration as being drawn to a non-elected invention. Claims 1-7, 9, 10, 13, and 14-16, 19-22 have been amended.

Claim 1 has been amended to recite that the ALA derivative crystals are "suspended in a polymer matrix" and wherein the ALA derivative crystals have a "mean diameter of 20μm to 200 μm." Support for the amendment to claim 1 can be found on page 4, lines 29-30 and page 5, line 30 of the specification as filed.

Claim 1 has been amended to recite "aminolaevulinic acid ester or a salt thereof." Support for this amendment can be found in orginal claim 10 and in the first paragraph of page 3 of the specification.

Claim 3 has been amended to correct the dependency. Claims 4, 6, 7, 9, 10, 13, 14-16, 19, and 21-22 have been amended to remove multiple dependencies.

Claims 6 and 7 have been amended to delete the term "finished" to provide correct antecedent basis. No new matter is added by this amendment.

Claims 7 and 19 have been amended to indicate the trademark for Eudragit® NE and to further provide its full chemical name, i.e., ethyl acrylate-methyl methacrylate-copolymerisate. No new matter is added by this amendment.

Claim 10 has been amended to recite "$R^2{}_2N\text{-}CH_2COCH_2\text{-}CH_2CO\text{-}OR^1$." The amendment is believed to correct the chemical formula $R^2{}_2N\text{-}CH_2COCH_2COOR^1$ that was lacking a CH_2 group. Applicants wish to thank the examiner for noticing this obvious error.

Claims 21 and 22 have been amended to reword the "use" claims into proper method claims. Support for this amendment can be found at least in the original claims in view of the

specification disclosing how ALA is used for photodynamic therapy and/or diagnosis of pre-cancerogenic and carcinogenic lesions of the skin.

Applicants have also amended the specification to recite the correct chemical formula "$R^2{}_2N\text{-}CH_2COCH_2\text{-}CH_2CO\text{-}OR^1$." The amendment to the specification is the same correction as that of claim 10. This is a correction of an obvious error and does not introduce new matter.

Applicants have also amended the specification to indicate the trademark for Eudragit® NE. No new matter is added by this amendment.

Summary of Interview

Applicants would like to thank Examiner Snigdha Maewall and Supervisor Dr. Kishore Gollamudi for their comments during the telephone interview of July 30, 2008 to discuss the Office Action mailed March 19, 2008. Applicants discussed the general strategy of replying to the office action, and discussed amending claim 1 consistent with the parent application US Application No. 10/332,547, where Applicants have encountered similar rejections and are responding by making amendments that include adding a lower particle size limitation and a recitation that the crystals are 'suspended' within the polymer matrix. It is believed that none of the cited references teach or suggest suspension of crystals at the recited sizes. Supervisor Gollamudi also posited that the demonstrated release rates could depend on the polymer used. Applicants noted that they have data for all three groups of the polymers specified in claim 3 in the specification and in Exhibits A and B submitted with the Declarations by Dr. Loebel under 37 C.F.R. § 1.132 executed in a related application (attached hereto), indicating that the unexpectedly higher ALA release rates are independent of the polymer matrix used.

Claim Objections

Claims 3-4, 6-7, 9-10, and 13-14 were objected to under 37 CFR § 1.75(c) as being in improper form because a "multiple dependent claim" shall refer to such other claims in the alternative only. Claim 3 has been amended to correct the dependency, and claims 3, 4, 6, 7, 9, 10, 12, 13, 14 and withdrawn claims 15, 16, 19, 21-22 have been amended to remove multiple dependencies.

Rejection Under 35 U.S.C. § 112, second paragraph

Claims 1-14 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Specifically, the Examiner has stated that "[c]laim 10 discloses a general formula for ALA derivative; however, CH_2 group is missing from the formula." As the examiner suggested, Applicants have amended the claim, and rewritten the formula.

Claims 1 was further rejected for reciting the phrase "less than approximately." Specifically, the Examiner has stated that the limitation "less than approximately" allegedly makes the claim indefinite, because "[i]t is not clear whether the limitation is less than or approximation." Applicants have amended the claim to recite "mean diameter of 20μm to 200 μm." Support for this amendment can be found on page four, lines 29-30 of the specification as filed. Applicants therefore respectfully request the withdrawal of this rejection.

Claim 10 was further rejected for reciting the phrase "optionally." Specifically, the Examiner has stated that the limitation "optionally" allegedly makes the claim indefinite, because "[i]t is not clear whether the limitation is really the limitation or not." Applicants respectfully traverse this rejection. As stated in the MPEP 2173.05(h):

> An alternative format which requires some analysis before concluding whether or not the language is indefinite involves the use of the term "optionally." In *Ex parte Cordova*, 10 USPQ2d 1949 (Bd. Pat. App. & Inter. 1989) the language "containing A, B, and optionally C" was considered acceptable alternative language because there was no ambiguity as to which alternatives are covered by the claim. A similar holding was reached with regard to the term "optionally" in *Ex parte Wu*, 10 USPQ2d 2031 (Bd. Pat. App. & Inter. 1989).

Another similar holding was reached with regard to the term "said optional substitution if present", in *Ex parte Holt*, 19 USPQ2d 1211 (Bd. Pat. App. & Inter. 1991), where claim 9 stated:

> The component of claim 1 wherein the thermotropic liquid crystalline polymer...consisting essentially of the recurring moieties I, II, and III which may include substitution of at least some of the hydrogen atoms present upon an aromatic ring...where Ar' is a divalent radical comprising at least one aromatic ring, with said optional substitution if present being selected from the group consisting of an alkyl group of 1 to 4 carbon atoms, an alkoxy group of 1 to 4 carbon atoms, halogen, a phenyl group and mixtures of the foregoing...

It was determined that "[t]he claims, however, clearly cover two embodiments, one wherein hydrogen atoms are present on the carbon atoms in an aromatic ring and another wherein carbon atoms are substituted with optional groups other than hydrogen." *Id.* Applicants submit that this is similar to the present application, wherein there are two embodiments: an ALA derivative wherein R^1 is an alkyl residue, and the other that is an ALA derivative wherein R^1 is an alkyl residue with substitutions and/or interruptions. Applicants therefore respectfully request the withdrawal of this rejection.

Rejection Under 35 U.S.C. § 103

A. Claims 1-6 and 8-14 were rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 95/05813 (WO 813), in view of US 5,856,566 ('566). Applicants respectfully traverse this rejection. The basis for this rejection is the allegation that WO 813 teaches a pharmaceutical composition comprising aminolevulinic acid (ALA) applied to the skin and indicates a desire for the ALA preparation to be stable due to the normally rapid degradation of ALA. The Office Action recognized that WO 813 does not teach crystalline ALA having a mean particle size

between 20 and 200 μm as recited in claim 1 or a mean particle size between 30 and 190 μm, or between 90 and 160 μm as recited in claims 4 and 5, respectively. In recognition of this deficiency in the teachings of WO 813, the Office Action alleges that "[i]n order to overcome the degradation problem, '566 suggests employing micronized crystals of ALA."

The present grounds of rejection fail to establish obviousness of the claims as amended for at least four reasons. Specifically, (1) the cited publications fail to describe or suggest ALA or ALA derivative crystals having the claimed sizes, (2) the cited publications fail to describe or suggest the use of ALA or ALA derivative crystals in a dermal application system as is claimed, (3) the cited publications fail to provide any reason to make or use micronized ALA or ALA derivative crystals in a dermal application system, and (4) Applicants have established that the described dermal application system exhibits the unexpected result of rapid release rates of ALA. Even accepting *arguendo* that WO 813 and '566 can properly be combined, WO 813 and '566, either alone or in combination, fail to disclose or suggest using ALA or ALA derivative crystals of the claimed sizes. Applicants have amended claim 1 to recite that the patch contains ALA derivative crystals which have a mean diameter of 20 μm to 200 μm. Support for this amendment can be found in the specification on page 4, lines 29-30. As noted by the Advisory Action, '566 teaches ALA or ALA derivative particles of a "few microns" for an investigation of the color of irradiated crystals, while WO 813 fails to disclose any ALA crystal size. In contrast, the instant claims require that the dermal application system contain ALA derivative crystals having a mean diameter of 20 to 200 μm, whereas neither WO 813 nor '566 teach or suggest ALA or ALA derivative crystals of a size range with a (mean) diameter of 20 to 200 μm as claimed, either independently, or specifically for use in a dermal application system. Applicants specifically note that crystals of a "few microns" are smaller than the smallest crystal size

required by the claims and nothing in either WO 813 or '566 suggest crystals in the claimed size range. For at least this reason, the claims are non-obvious.

The combination of WO 813 and '566 also fail to disclose or suggest the use of ALA or ALA derivative crystals in a dermal application system. Although WO 813 discloses a pharmaceutical composition comprising non-crystalline ALA, it does not disclose or suggest the suspension of crystalline ALA into the matrix, and although '566 discloses crystalline ALA or ALA derivatives, it does not disclose or suggest the suspension of crystalline ALA or ALA derivatives into a matrix. Instead, WO 813 discloses dissolving ALA into the matrix prior to gel formation (see page 12, Example 2, line 3), and '566 describes only storage of crystalline ALA or ALA derivatives and suggests dissolving the ALA or ALA derivative crystals in water (see column 3, lines 1-4). This is in clear contrast to the claimed composition, which requires a polymer matrix containing crystalline ALA derivatives. Page 5, line 30 of the present specification indicates that the ALA or ALA derivative is "dispersed/suspended in the polymer matrix." Thus, even if the skilled artisan were motivated to combine the teachings of WO 813 and '566 to produce a dermal application system using ALA or ALA derivative crystals of a few microns, this combination would not result in the claimed composition since the skilled artisan would be led to dissolve the ALA or ALA derivative into the matrix. And, because crystals cease to be crystals when dissolved, the resulting composition would therefore not comprise ALA or ALA derivative crystals as claimed. For at least this reason, the claims are non-obvious.

Further, WO 813 and '566 fail to provide any reason to make or use micronized ALA or ALA derivative crystals, let alone crystals with a size of 20-200 μm, in a dermal application system. For example, the skilled artisan would not have been motivated to stabilize ALA by micronizing ALA. While WO recognizes that ALA preparations are unstable, they solve this

problem by adding a stabilizing amount of a saccharide or an organic weak protein donor (e.g., claim 7 or claim 11, abstract, page 3, lines 14-20, page 4, lines 1-4, and 25-29). And, because '566 teaches that ALA crystals should be irradiated to obtain crystals with enhanced stability, even if *arguendo* the skilled artisan were motivated to combine WO with the teachings of '566 to increase the stability of ALA or ALA derivatives, the skilled artisan might have irradiated ALA and added a stabilizing amount of a saccharide or an organic weak protein donor. '566 does not teach that micronization had any beneficial effect, including stability, but only investigates optical characteristics by means of these crystals. The artisan would thus not have modified the prior art, which taught to dissolve the ALA in the matrix. He/she would thus not arrive at the claimed composition comprising suspended crystals of defined size. Thus, WO and '566 fail to provide a reason to use micronized ALA crystals in a dermal application system. For at least this reason, the claims are non-obvious.

Furthermore, even if *arguendo* the Office establishes *prima facie* obviousness, Applicants have provided sufficient evidence of unexpected results to rebut a finding of obviousness. Specifically, the use of ALA or ALA derivative crystals with a size of 20 to 200 μm in the claimed dermal application system are non-obvious due to unexpectedly higher ALA release rates. As shown in Exhibit A and Exhibit B of the attached Declarations under 37 C.F.R. § 1.132 by Mechtild Loebel, which were/will be submitted in related Application No. 10/332,457, the rate of ALA crystal release is dramatically higher than what is observed in prior art dermal application systems using dissolved ALA.

Specifically, 515 $\mu g/cm^2$ ALA was released/ permeated from a silicon polymer patch comprising ALA crystals (90-160 μm in size) in the first hour, whereas only 9 $\mu g/cm^2$ ALA was released and had permeated through an artificial membrane when dissolved ALA was used (see

Figure 1 of Exhibit A). Likewise, about 1500 μg/cm^2 of ALA were released/ permeated from a polyacrylate patch comprising ALA crystals (20 to 200 μm in size) in the first hour, with 72.5 % of all ALA released in the first 30 min (see Figure 2A of Exhibit A). Moreover, as shown in Figure 1 of Exhibit B, about 1000 μg/cm^2 (57%) of ALA was released/ permeated from a polyisobutylen polymer patch comprising ALA crystals (90-160 μm in size) in the first hour. Therefore, the rate of ALA release from polymer matrices comprising ALA crystals is dramatically higher than what is observed in prior art dermal application systems using dissolved ALA. Moreover, these results indicate that the unexpectedly higher ALA release rates are independent of the polymer matrix used.

Note that in Figure 2A of Exhibit A, 72.5% of all ALA is released in 30 min. Therefore, it can be estimated from the Figure that approximately 92.5% is released by 2 hours. 92.5% in 2 hours is surprising when compared to the amount released from a "dissolved" ALA patch as shown in Figure 1 of the declaration. It can also be argued that if 92.5% of the patch in Figure 2A of Exhibit A is released in 2 hours, this must contain particles across the entire size range of 20-200 μm, as none of the bars in Figure 2B of Exhibit A are less than approximately 7.5%.

Demonstration of unexpected results is a secondary consideration akin to commercial success and long felt need, and it is sufficient to demonstrate that the superior features of the claimed composition were not predicted. For at least this reason, the claims are non-obvious. For all of the above reasons, Applicants submit that the present claims are not obvious in view of the cited publications and therefore respectfully request the withdrawal of the present rejection and allowance of claims 1-14.

B. Claims 1-6 and 8-14 were rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 95/05813 (WO 813), in view of US 5,856,566 ('566), and further in view of WO 97/10811

(WO 811) and US Patent pub. 2004/0171881 ('881). Apparently recognizing that WO 813 and '566 do not teach crystalline ALA or ALA derivatives having a mean particle size between 20 and 200 μm, the Office Action attempts to overcome this deficiency by demonstrating a motivation in the art for use of nano-crystaline formulations. Specifically, the Office Action alleges that "'881 discloses that nano crystalline formulations typically afford greater bioavailability of drug compounds (see paragraph [1426]) and WO '811 discloses the benefit of enhancing solubility and use of nano particles in photodynamic therapy (abstract title and page 3, first paragraph)." Applicants respectfully traverse this rejection.

As noted above, the combination of WO 813 and '566 do not teach or suggest the suspension of crystalline ALA or ALA derivatives at the clamed sizes in a polymer matrix, and WO 811 and '881 do not correct these deficiencies.

WO 811 details a methodology to solubilize zinc phthalocyanine complex in an aqueous solution using nanoparticles, because zinc phthalocyanine complex is "characterized by extremely low water solubility and insolubility in almost all organic solvents." WO 811 solves the problem of poor water solubility of zinc phthalocyanine complexes by addition of a polymer support which – mixed with the active agent – is provided in the form of nanoparticles and can be dissolved, which is necessary for intravenuous administration. There is no connection to the problem of stability of ALA in aqueous solutions. In contrast to the intravenuous application of zinc phthalocyanine complexes in WO 811, the present application relates to a transdermal application system. Furthermore, ALA salt is readily soluble in aqueous solutions. One of skill in the art would thus not rely on this reference to correct the deficiencies of WO 813 and '566, since the nanoparticles of WO 811 were described to solve a problem not relevant to the ALA

transdermal system of WO 813. Thus, there was no reason in the prior art to combine WO 811 with WO 813 and '566.

Moreover, had one skilled in the art actually combined these references, one would have arrived at a composition distinctly different from the claimed dermal application system. The claims of the present application are directed to ALA derivative crystals of specific size "dispersed/ suspended" in a non-aqueous polymer solution and then dried as a patch for dermal delivery. The ALA derivative crystals of the invention are not encapsulated in nanospheres, and the ALA derivative crystals are not solubilized in an aqueous solution, but dispersed/suspended as crystals in a polymer matrix prior to drying.

Moreover, "nanoparticles" are defined in the WO 811 specification as "solid spheroid particles ranging in size from about 10 to 1000 nm.". The nanoparticles of WO 811 are not crystals, but mixtures of active agent and polymer in particulare form. The size range of these nanoparticles (0.01 to 1 μm) is well below that of the presently claimed ALA derivative crystals (20 to 200 μm). For at least this reason, the claims are non-obvious.

The '881 application does not add anything to the previously discussed publications. U.S. Pat. Nos: 5,145,684 and 6,045,829, patents cited by '881 for preparations of nano-crystal dispersion formulations, also use nano-crystals to solve the problem of poor gastrointestinal absorption of a drug by increasing the drug's surface area by adding "a surface modifier adsorbed on the surface" (5,145,684) or "a cellulosic surface stabilizer" (6,045,829) to the crystals. As patent 5,145,684 states:

> Poorly water soluble drugs, i.e., those having a solubility less than about 10 mg/ml, tend to be eliminated from the gastrointestinal tract before being absorbed into the circulation. Moreover, poorly water soluble drugs tend to be unsafe for intravenous administration techniques, which are used primarily in conjunction with fully soluble drug substances. It is known that the rate of dissolution of a particulate drug can increase with increasing surface area, i.e., decreasing particle size. Consequently,

> methods of making finely divided drugs have been studied and efforts have been made to control the size and size range of drug particles in pharmaceutical compositions.

As discussed above, in the context of the present invention, ALA is not to be administered intravenuously, but transdermally, so the fundamental problem is different. Furthermore, '881 also refers to nanoparticles much smaller that the crystal having a size of 20-200 μm incorporated in the dermal application system of the invention.

For all of the above reasons, Applicants submit that the present claims are not obvious in view of the cited publications and therefore respectfully request the withdrawal of the present rejection and allowance of claims 1-6 and 8-14.

C. Claims 1-6 and 8-14 were rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 96/06602 (WO 602), in view of US 5,856,566 ('566). Applicants respectfully traverse this rejection. The examiner has suggested that WO 602 teaches a pharmaceutical composition comprising aminolevulinic acid (ALA) and ALA derivatives applied to the skin, and indicates a desire for the ALA or ALA derivative preparation to be stable due to the normally rapid degradation of ALA. The Office Action recognized that WO 602 does not teach crystalline ALA or ALA derivatives having a mean particle size between 20 and 200 μm as recited in claim 1 or a mean particle size between 30 and 190 μm, or between 90 and 160 μm as recited in claims 4 and 5, respectively. In recognition of this deficiency in the teachings of WO 602, the Office Action alleges that "[i]n order to overcome the degradation problem, '566 suggests employing micronized crystals of ALA."

WO 602 is a continuation-in-part of PCT/US94/09466 (WO 813). As there are no disclosures in WO 602 that correct the deficiencies of the combination of WO 813 in view of '566, as described in section A above, Applicants traverse this rejection for the reasons stated above in section A. Applicants therefore respectfully request the withdrawal of this rejection.

D. Claims 1-6 and 8-14 were rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 96/06602 (WO 602), in view of US 5,856,566 ('566), and further in view of WO 97/10811 (WO 811) and US Patent pub. 2004/0171881 ('881).

WO 602 is a continuation-in-part of PCT/US94/09466 (WO 813). As there are no new disclosures in WO 602 that correct the deficiencies of the combination of WO 813, in view of '566, and further in view of WO 811 and '881 as described in section B above, Applicants traverse this rejection for the reasons stated above in section B. Applicants therefore respectfully request the withdrawal of this rejection.

E. Claim 7 is rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 96/06602 (WO 602) or WO 95/05813 (WO 813), in view of US 5,856,566 ('566), WO 97/10811 (WO 811) and US PG pub. 20040171881 ('881), and further in view of US 5,456,745 ('745).

The Office Action recognizes that '566 does not teach the claimed polymer and softener. In recognition of this deficiency, the Office Action alleges that '745 teaches "flexible film forming gels made of polymeric materials such as Eudragit, cellulose, gums ... containing moisturizers, softeners such as citric acid esters ... and exhibits adhesive properties..." Thus, The Examiner alleges that acrylate polymers containing softeners such as citrate esters are known in the art.

Applicants traverse this rejection for the reasons stated above. Specifically, none of the references teach suspension of ALA derivative crystals in a polymer matrix having a mean particle size between 20 and 200 μm. The disclosure of '745 does not correct these deficiencies. Applicants therefore respectfully request the withdrawal of this rejection.

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to

directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

A Credit Card Payment submitted via EFS-WEB authorizing payment in the amount of $525.00, representing the fee for a small entity under 37 C.F.R. § 1.17(a)(3) for a Three Month Extension of Time, a Request for Extension of Time, a Declaration under 37 C.F.R. § 1.132 by Mechtild Loebel with Exhibit A attached, and a Declaration under 37 C.F.R. § 1.132 by Mechtild Loebel with Exhibit B attached are hereby enclosed. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

Brian Giles

P. Brian Giles, Ph.D.
Registration No. 57,896

BALLARD SPAHR ANDREWS & INGERSOLL
Customer Number 23859
(678) 420-9300
(678) 420-9301 (fax)

CERTIFICATE OF ELECTRONIC TRANSMISSION UNDER 37 C.F.R. § 1.8			
I hereby certify that this correspondence, including any items indicated as attached or included, is being transmitted via electronic transmission via EFS-Web on the date indicated below.			
Name of Person Mailing	P. Brian Giles, Ph.D.		
Signature	Brian Giles	Date	9-17-2008